GENETIC CONTROL OF HIGH DENSITY AND LOW DENSITY LIPOPROTEINS AS A FUNCTION OF DIET AMONG INBRED MICE SUSCEPTIBLE AND RESISTANT TO ATHEROSCLEROSIS -- Dr. Renee C. LeBoeuf

The long term goal of this research project is to define genetic and metabolic factors involved in the development of atherosclerosis. This disease is the leading cause of mortality in the Western world and its risk of onset appears to be influenced by nutritional and genetic factors. In fact, nutritional experiments in man and animals have confirmed that dietary lipid is an important factor influencing serum cholesterol levels and heart disease. The hereditary component in atherosclerosis is likely to be complex and characterized by the involvement of a large number of genes, many of which pariticipate in determining the levels and structures of plasma lipoproteins which carry cholesterol.

This proposal uses the tools of genetics, biochemistry and molecular biology to characterize the regulation of lipid transport genes by defined diets. The mouse is the best system for genetic studies because of the well characterized chromosomal map and special genetic tools. In contrast, only limited aspects of the genetic regulation of lipoproteins can be examined directly in humans because of environmental factors and genetic heterogeneity among human populations. The diets to be used include those containing cholesterol, saturated, polyunsaturated and monounsaturated fats, fish oils, and certain combinations of these lipids.

The specific aims of this proposal are:

1. Identify and characterize genetic variations among inbred mouse strains for activities and messenger RNA (mRNA) levels of enzymes and receptors known to control HDL levels. Mice fed low and high-fat diets will be used to examine hepatic lipase, lecithin:cholesterol acyltransferase, the HDL efflux receptor on non-hepatic tissues and the hepatic HDL uptake receptor.

2. Characterize changes in LDL levels among inbred strains fed low and high-fat diets. Apart from the LDL-receptor, the genetic regulation of plasma LDL concentrations is not well defined.

3. Determine the number and chromosomal location of genes regulating levels of LDL in mice.

4. Determine whether or not changes in gene regulation of HDL and LDL upon fat feeding correlate to lesion formation.

The information obtained from this work will shed light on basic factors controlling lipid tansport and atherosclerosis.